REMARKS

Claims 1, 5, 7, 8, 10-19, 32, 46-48 and 50 were examined in the Office Action under reply and were rejected under (1) 35 U.S.C. §102(b) (claims 1, 5, 19, 32, 46, 48 and 50); and (2) 35 U.S.C. §103(a) (claims 7, 8, 10-18, 46 and 47). These rejections are believed to be overcome for reasons discussed below.

Applicants note with appreciation the withdrawal of the previous rejection under 35 U.S.C. §112, first paragraph.

Overview of the Above Amendments:

Claim 1 has been amended herein to recite the subject invention with greater particularity. Specifically, claim 1 clarifies that the N-terminus of the N-terminally deleted NS3 polypeptide is at an amino acid that corresponds to amino acid 1242 of the HCV-1 polyprotein. Other minor wording changes have been made to the claim for clarity. Support for the amendments can be found throughout the specification at e.g., page 55, line 13 and in Figures 5, 11, 14, 17, 18, 21 and 22 where the N-terminus of the mutant NS3 polypeptide is amino acid 1242. The foregoing amendments are made without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record.

Rejections Under 35 U.S.C. §102(b):

Claims 1, 5 and 19 were rejected under 35 U.S.C. §102(b) as anticipated by Bartenschlager et al., *J. Virol.* (1993) 67:3835-3844 ("Bartenschlager"). The Office argues Bartenschlager discloses an N-terminally truncated NS3 polypeptide with amino acids 1116-2344 of the HCV polyprotein "which encompasses Applicant's polypeptide comprising amino acids 1242-1657." Office Action, page 3. However, applicants respectfully submit that Bartenschlager fails to anticipate the claimed invention.

In order to be anticipatory, a single reference must disclose each and every element of the claims. *See, e.g., Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986). Moreover, the single source must disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989). Bartenschlager fails to disclose each and every element of applicants' claimed invention and therefore does not anticipate applicants' claims.

In particular, the pending claims are directed to mutant NS HCV polypeptides comprising a mutant NS3 polypeptide wherein the mutant NS3 polypeptide has an N-terminus at an amino acid corresponding to amino acid 1242 of HCV-1 and comprises an amino acid sequence corresponding to amino acids 1242-1657 of HCV-1. Nowhere does Bartenschlager describe such a polypeptide. As recognized by the Examiner, the N-terminus of one of Bartenschlager's molecules is amino acid 1116. Two other truncated constructs described in Bartenschlager have N-termini at positions 1142 (nucleotide position 3426) and 1151 (nucleotide position 3453). See, page 3839, last paragraph of Bartenschlager. Thus, Bartenschlager's truncated molecules are different from applicants' mutant NS3 polypeptide. Accordingly, the pending claims are not anticipated by Bartenschlager and withdrawal of this rejection is respectfully requested.

Claims 1, 19, 32, 46, 48 and 50 were rejected under 35 U.S.C. §102(b) as anticipated by EP Publ. No. 693,687 to Houghton et al. ("Houghton"). The Office alleges: "Houghton discloses combinations of HCV antigens for use in immunoassays to detect anti-HCV antibodies...Since Houghton teaches SEQ ID NO:9, and Applicant claims that the mutant NS3 polypeptide can comprise/consist of SEQ ID NO:9, then the claims are anticipated." Office Action, pages 3-4, bridging paragraph. However, applicants respectfully disagree with the Office's assessment.

Contrary to the Office's statements, Houghton does not teach the sequence of SEQ ID NO:9. In particular, Figure 1 of Houghton, referred to by the Examiner, is a figure of the **entire** polyprotein (see, page 3, lines 28-29 of Houghton). SEQ ID NO:9, on the other hand, only includes amino acids 1242-3011 of the HCV polyprotein (plus an N-terminal Met). The NS3 fragments described in Houghton are C33c, which consists of amino acids 1192-1457 of the HCV-1 polyprotein and C100, which consists of amino acids 1569-1931 of the HCV-1 polyprotein. There is no disclosure regarding an N-terminally truncated NS3 with an N-terminus at amino acid 1242 as claimed. Thus, Houghton also fails to anticipate the claimed invention and withdrawal of this basis for rejection is respectfully requested.

Rejections Under 35 U.S.C. §103:

Claims 7, 8, 10-18, 46 and 47 were rejected under 35 U.S.C. §103(a) as unpatentable over Bartenschlager in view of Houghton et al. The Office recognizes that Bartenschlager fails to teach the use of NS4a, NS4b, NS5a, NS5b, C and E proteins fused with NS3. Houghton is cited for disclosing combinations of HCV antigens for use in immunoassays to detect antibodies. The Office asserts: "It would be obvious to incorporate the antigens of Houghton into the truncated NS3 polypeptide of Bartenschlager." Office Action, page 4. However, applicants disagree with the Office's reasoning.

In particular, in order to support a *prima facie* case of obviousness, the prior art must suggest making the specific molecular modifications necessary to achieve the claimed invention. See, *In re Deuel*, 34 USPQ2d 1210, 1214; *In re Jones*, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990); *In re Grabiak*, 226 USPQ 870, 872 (Fed. Cir. 1985) ("[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/ [claimed] thioester change in structure, in order to complete the PTO's *prima facie* case and shift the burden of going forward to the applicant."); *In re Lalu*, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). Here, neither a reading of Bartenschlager alone, or in combination with Houghton renders the claimed molecular modifications obvious.

As explained above, Bartenschlager, the primary reference, does not describe a mutated NS3 molecule with an N-terminus at amino acid 1242. Rather, Bartenschlager describes molecules with internal deletions, as well as three constructs with N-terminal deletions resulting in molecules with N-termini at amino acids 1116, 1142 and 1151. There is simply no suggestion in Bartenschlager to produce the specific molecule claimed by applicants. Nor does this reference teach or suggest mutants in which the catalytic domain is disrupted due to the deletions. Indeed, with regard to the internal deletions, Bartenschlager states "we cannot decide whether the [internal] deletions affected the proteinase activity or accessibility of the cleavage site..." (See, page 3840, second column). Additionally, Bartenschlager does not address whether his deletion mutants, let alone applicants' claimed deletion mutant, results in an immunogenic molecule. Thus, Bartenschlager fails entirely to teach or suggest mutant NS3-containing polypeptides having the claimed characteristics.

Houghton does not provide the missing link. Like Bartenschlager, Houghton does not teach or suggest the NS3 mutant as claimed. Houghton is directed to combination HCV antigens comprising an antigen from the core domain of HCV and an additional HCV antigen. A preferred antigen from the NS3 domain specified in Houghton is C33c. C33c includes amino acids 1192-1457 of NS3. There is no suggestion in Houghton to make the particular deletion to the N-terminus of the NS3 claimed by applicants (namely, a deletion resulting in an NS3 mutant with an N-terminus at amino acid 1242 of HCV-1) and to retain the C-terminal portion of the NS3 domain.

Applicants discovered that polypeptides including the deletion specified in the claims still retained immunogenicity. There was absolutely no expectation based on the cited art that HCV NS mutant polypeptides, having a deletion resulting in an NS3 mutant with an N-terminus at 1242, would function as claimed.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified, does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Without a suggestion to modify the references evident in the prior art as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Based on the foregoing, the rejection of the claims over the stated combination should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are patentable over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Please direct all further communications in this application to:

Michael J. Moran
Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2969
Facsimile: (510) 655-3542.

Respectfully submitted,

Date: 2/7/05

By: _____
Roberta L. Robins
Registration No. 33,208
Attorney for Applicants

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097